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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/047,253	01/14/2002	Gregory Cope	CIT1510-4	6270

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/047,253	COPE ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,33,36,37,41-57,74,75,77 and 78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-33, 36-37, 41-57, 74-75 and 77-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The after final amendment filed on December 2, 2005, amending claim 32 and 77 and adding claims 78, has been entered.

Claims 32-33, 36-37, 41-57, 74-75 and 77-78 are pending and are under consideration.

Response to Arguments

Applicant's arguments with respect to claims 37-40, 42-46, 48-66 and 87-88 have been considered but are moot in view of the new ground(s) of rejection. Therefore, the finality of the last Office action is withdrawn.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that the sequences in Figure 1-4 lack sequence identification numbers. See particularly 37 CFR 1.821(d).

Claim Objections

Claims 32 and 78 are objected to because of the following informalities: Claim 32 recites phrases with unnecessary hypens or underlines, for example: "the-isopeptidase", "affects-isopeptidase", "agent-that" and "isopeptidase activity agent_by" Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32 and 78 and claims 33, 36-37, 41-57, 74-75 and 77 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32 and 78 recite the phrase "Accession Nos: NP_116659; NP 005796; and O00487" and "Accession No.: JC7985 and AAD05037". The metes and bounds of these phrase in the context of the claims are not clear. Amino acid sequences of proteins having Accession number can change or be deleted. Therefore, it is unclear from the specification or from the claim as to which specific amino acid sequence Rpn11 or AMSH has. Examiner requests clarification. Furthermore, the provision of accession numbers instead of SEQ ID NO: precludes the examiner from doing a meaningful search. Therefore, Examiner suggests providing SEQ ID NO:, provided applicants have ample support.

Claims 32 and 78 and claims 33, 36-37, 41-57, 74-75 and 77 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32 and 78 recite the phrase "identifying an agent " and "test agent". It is not clear to the Examiner if the "agent" and "test agent" are the same. If they are the same, Examiner requests amendment of the claims to recite either "agent" or "test agent" to maintain uniformity amongst the claims.

Claims 32 and 78 and claims 33, 36-37, 41-57, 74-75 and 77 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32 and 78 recite the phrase "determining the isopeptidase activity agent by measuring deconjugation of the modifier protein from the target protein". The metes and bounds of the phrase in the context of the above claims is not clear to the Examiner. It is not clear to the Examiner as to what applicants mean by "determining the isopeptidase activity agent". Furthermore, it is also not clear as to how those skilled in the art can conclude that the agent identified by the above method modulates isopeptidase activity of Rpn11 or AMSH. It is not clear to the Examiner as to how applicants or those skilled in the art would recognize that said agent being tested is indeed specifically affecting isopeptidase activity of Rpn11 or AMSH and not directly causing the cleavage of the modifier protein from the target protein without affecting the isopeptidase. Therefore, the method lacks essential step(s). Furthermore, since applicants do not indicate that the reaction comprises a target protein which indeed comprises a modifier protein, said target protein and modifier protein lacks antecedence

within the a claim. It is also not clear whether the target protein inherently comprises the modifier protein or whether it is added separately.

Claims 32 and 78 and claims 33, 36-37, 41-57, 74-75 and 77 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32 and 78 recite the phrase "determining the isopeptidase activity by measuring deconjugation". The metes and bounds of the phrase in the context of the above claim is not clear to the Examiner. t is not clear to the Examiner how "measuring deconjugation" of the modifier protein from the target protein leads one of ordinary skill in the art to conclude that a test agent causes a change in isopeptidase activity of Rpn11 or AMSH or what applicants mean by "measuring deconjugation". This is because the method does not recite steps of distinguishing cleavage of modifier proteins from target proteins in the presence of test agents that reduce isopeptidase activity of Rpn11 or AMSH and test agents that do not modulate isopeptidase activity of Rpn11 or AMSH, since test agents that modulate isopeptidase activity of Rpn11 or AMSH do not ameliorate isopeptidase activity, but can merely reduce isopeptidase activity of Rpn11 or AMSH Therefore, the method lacks essential step(s).

Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 recites the phrase "an amino acid sequence of SEQ ID NO:2". The metes and bounds of this phrase in the context of the above claim are not clear to the Examiner. It is not clear whether the JAMM domain comprises a fragment of SEQ ID NO:2 or the full length of the amino acid sequence of SEQ ID NO:2. A perusal of the specification did not provide the Examiner with a specific definition for the above phrase. As applicants have not provided a definition for the above phrase, Examiner has interpreted the claims broadly to mean that a JAMM domain consisting essentially of "an amino acid of SEQ ID NO:2" encompasses fragments of SEQ ID NO:2. Examiner requests clarification of the above phrase and suggests amending the claim by replacing "an" with "the" in the above phrase.

Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 recites the phrase "not conjugated to the modifier protein". The metes and bounds of the phrase in the context of the above claim is not clear to the Examiner. It is not clear to the Examiner which protein applicants are referring to. It appears that applicant s are actually referring to "target protein deconjugated from the modifier protein:. IF this is so, amending the claim accordingly would overcome this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-33, 36-37, 41-57, 74-75 and 77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 32-33, 36-37, 41-57, 74-75 and 77 are drawn to a method of identifying an agent that affects isopeptidase activity of a polypeptide, wherein the polypeptide is Rpn11 "Accession Nos.: NP005796 and O00487". However, these polypeptides were not described in the application as originally filed nor in any of its parent applications. Therefore, claims 32-33, 36-37, 41-57, 74-75 and 77 contain new matter.

Given this lack of description of the polypeptides having Accession Nos: NP005796 and O00487", the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 32-33, 36-37, 41-57, 74-75 and 77 at the time of filing of the instant application.

Claims 32-33, 36-37, 41-57, 74-75 and 77-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 32-33, 36-37, 41-57, 74-75 and 77-78 are drawn to a method of identifying an agent that modulates isopeptidase activity of Rpn11 or AMSH by contacting (1) a Rpn11 or AMSH having isopeptidase activity with a test agent, (2) a target protein inherently comprising a modifier protein, wherein in the absence of the test agent, Rpn11 or AMSH cleaves said modifier protein from said target protein. These claims encompass a method of using any or all Rpn11 complex or AMSH polypeptides and any target proteins, including recombinants, mutants and variants, which are isolated from any source. Therefore, these claims are drawn to a method of using a genus of Rpn11 complex having any structure or AMSH polypeptides, a genus of target proteins having any structure comprising a genus of modifier proteins having any structure, including any or all recombinants, mutants or variants. Said genus comprising any or all Rpn11 complex or AMSH may or may not cleave any target proteins or those recited in the claims. The specification only describes a method of identifying agents that modulate isopeptidase activity of a Rpn11 of Accession No. NP116659 by contacting said Rpn11 with ubiquitin and Sic1, as described in Example 1 of the specification. One species is not enough to describe the whole genus and there is no evidence on the record of the relationship between the structure of the Rpn11 of

Accession No. NP116659 and the structure of any Rpn11 from any source, including any or all recombinants, mutants and variants thereof. Similarly, there is no evidence on the record of the relationship between the structure of ubiquitin and Sic1 and the structure of any modifier proteins and target proteins, respectively. Therefore, the specification fails to describe a representative species of the genus comprising any or all Rpn11 complex or AMSH, genus comprising any or all modifier proteins and genus comprising any or all target proteins, including any or all recombinants, mutants or variants thereof, wherein said genus of Rnp11 complex or AMSH cleaves said genus of modifier proteins from said genus of target proteins in the absence of a test agent, that can be used to identify agents that modulate the isopeptidase activity of Rnp11 complex or AMSH.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 32-33, 36-37, 41-57, 74-75 and 77-78.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants should note that the rejection has been amended.

Applicants argue that the instant claims are fully described because claim 32 and 78 have been amended to recite a specific amino acid sequence via Accession numbers for Rpn11 and AMSH. However, claim 32 remains drawn to a "Rpn11 complex" having any structure. Also, these claims remain drawn to a method of using a genus of Rpn11 complex having any structure or AMSH polypeptides, a genus of target proteins having any structure comprising a genus of modifier proteins having any structure, including any or all recombinants, mutants or variants, wherein said genus comprising any or all Rpn11 complex or AMSH may or may not cleave any target proteins or those recited in the claims. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species

disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only a few species within the genus. In the instant case the claimed genera of the claims includes species which are widely variant in structure. The claims are drawn to structurally diverse species as it encompasses any or all Rpn11 complexes, the recited Rpn11, and the recited AMSH, and such diverse species comprising different structure have not been described. As such, the description of solely functional features present in all members of the genus is insufficient to be representative of the attributes and features of the entire genus.

Claims 32-33, 36-37, 41-57, 74-75 and 77-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying agents that modulate isopeptidase activity of a Rpn11 of Accession No. NP116659 by contacting said Rpn11 with ubiquitin and Sic1, as described in Example 1 of the specification, does not reasonably provide enablement for a method of identifying agents that modulate isopeptidase activity of Rpn11 complex or AMSH having any structure using modifier and target proteins having any structure, including any or all recombinants, mutants or variants of the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,

1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 32-33, 36-37, 41-57, 74-75 and 77-78 are drawn to a method of identifying an agent that modulates isopeptidase activity of Rpn11 complex or AMSH by contacting (1) a Rpn11 complex or AMSH having isopeptidase activity with a test agent wherein said Rpn11 complex or AMSH comprise variants, mutants and recombinants of the same, (2) a target protein inherently comprising a modifier protein, wherein in the absence of the test agent, Rpn11 complex or AMSH cleaves said modifier protein from said target protein. However, these claims encompass a method of using any or all Rpn11 complex or AMSH polypeptides to cleave any target proteins comprising a modifier protein isolated from any source and having any structure, including recombinants, mutants and variants, any modifier proteins or those recited in the claims from any target proteins or those recited in the claims. Therefore, the claims are drawn to a method of identifying agents that modulate isopeptidase activity of any or all Rnp11 complex having any structure or AMSH using target and modifier proteins having any structure.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of Rpn11 complex or AMSH, target and modifier proteins broadly encompassed in the claimed method, wherein said

Rpn11 complex or AMSH may or may not cleave said target proteins from said modifier proteins. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

However, in this case the disclosure is limited to a method of identifying agents that modulate isopeptidase activity of a Rpn11 of Accession No. NP116659 by contacting said Rpn11 with ubiquitin and Sic1, as described in Example 1 of the specification, but provides no guidance with regard to a method of identifying agents that modulate any or all Rpn11 complex or AMSH by contacting said Rpn11 complex or AMSH with any or all target proteins or any or all modifier proteins. It would require undue experimentation of the skilled artisan to make and use the agents in the claimed method. In view of the great breadth of the claim, amount of experimentation required to identify and make the polypeptides, amount of experimentation required to identify a Rpn11 complex or AMSH that cleaves any or all modifier protein from any or all target protein, the lack of guidance, working examples, and/or unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the proteins to identify agents that modulate isopeptidase activity of a Rpn11 complex or AMSH.

While enzyme isolation techniques, recombinant and mutagenesis techniques and other related techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications in a polypeptide as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a method of identifying agents that modulate isopeptidase activity of Rpn11 complex or AMSH by contacting a said Rpn11 complex or AMSH with any or all modifier and target proteins, including any or all recombinants, mutants or variants, because the specification does not establish: (A) a universal method to identify agents that modulate isopeptidase activity of any or all Rpn11 complex or AMSH by contacting a said Rpn11 complex or AMSH with any or all modifier and target proteins; (B) regions of a Rpn11 complex or AMSH which may be modified without affecting its isopeptidase activity; (C) the general tolerance of Rpn11 complex or AMSH to modification and extent of such tolerance; (D) a rational and predictable scheme for selecting any Rpn11 complex or AMSH, target and modifier proteins with an expectation of the Rpn11 complex or AMSH cleaving said target protein from said modifier protein; and (E) the specification provides

insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of identifying agents that modulate isopeptidase activity of any or all Rpn11 complex or AMSH by contacting a said Rpn11 complex or AMSH with any or all modifier and target proteins. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of Rpn11 complex or AMSH, modifier and target proteins having the desired biological characteristics used in the method and Rpn11 complex or AMSH that cleaves a modifier protein from a target protein is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office Action, applicants have traversed the above rejection. Applicants should note that the rejection has been amended.

Applicants argue that the instant claims are fully described because claim 32 and 78 have been amended to recite a specific amino acid sequence via Accession numbers for Rpn11 and AMSH. However, claim 32 remains drawn to a "Rpn11 complex" having any structure and furthermore, because applicants have not provided a SEQ IDNO: for the sequences, Examiner was unable to perform a meaningful search. Also, these claims remain drawn to a method of using a genus of Rpn11 complex

having any structure or AMSH polypeptides, a genus of target proteins having any structure comprising a genus of modifier proteins having any structure, including any or all recombinants, mutants or variants, wherein said genus comprising any or all Rpn11 complex or AMSH may or may not cleave any target proteins or those recited in the claims. Therefore, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the use of Rpn11 complex or AMSH that cleaves an extremely large number of any or all modifier protein from any or all target protein, broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and a detailed knowledge of the ways in which the proteins' structure relates to its function. It is this specific guidance that applicants do not provide. Without specific guidance, those skilled in the art will be subjected to undue experimentation of identifying a Rpn11 complex or AMSH that cleaves any or all modifier protein from any or all target protein that results from such experimentation.

Hence the rejection is maintained.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935.

The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652

Manjunath Rao
Primary Patent Examiner 1652